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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/674,414	10/01/2003	Minoru Ueda	TEI-0128	5142

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EXAMINER	
FORD, ALLISON M	

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 01/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/674,414	UEDA ET AL.	
	Examiner	Art Unit	
	Allison M Ford	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 7-9* is/are pending in the application.

4a) Of the above claim(s) *7-9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election of claims 1-3 in the reply filed on 11/24/2004 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 1-3 and 7-9 are pending in the current application; claims 7-9 are withdrawn from consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant has failed to provide evidence to show they were in possession of a method of accelerating the differentiation of undifferentiated mesenchymal cells to chondrocyte cells. Applicant's experimental evidence shows that after 10 days of culture chondrocytes were produced; those chondrocytes exposed to ultrasound in Experimental Group 3 (+TGF-β/ +ultrasound) produced 15% more protein then cells in Control Group 1 (-TGF- β/ -ultrasound), and 10% more protein than cells in Control Group 2 (+TGF- β/ -ultrasound) (See Specification Pg. 9). Applicant's data only shows that chondrocytes exposed to ultrasound had increased aggrecan protein production; there is no evidence or teachings on the rate at which the original

undifferentiated mesenchymal cells differentiated into chondrocytes. Therefore applicant has only taught a method of increasing aggrecan protein production by applying ultrasound to cultures of chondrocytes, which is clearly taught in the prior art (See, e.g., Nishikori et al and Parvizi et al). Therefore there is not sufficient evidence to show applicant was in possession of a method of accelerating the differentiation of undifferentiated mesenchymal cells to chondrocyte cells.

Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for increasing expression of aggrecan in chondrocyte cells, does not reasonably provide enablement for accelerating the differentiation of undifferentiated mesenchymal cells to chondrocyte cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Applicant correlated aggrecan expression to rate of differentiation of undifferentiated mesenchymal cells to chondrocyte cells. While it is enabled for ultrasound treatment to increase the expression of aggrecan, it is not enabled for the ultrasound treatment to accelerate differentiation of undifferentiated mesenchymal cells to chondrocyte cells. The assertion that ultrasound treatment accelerates differentiation of undifferentiated mesenchymal cells to chondrocyte cells cannot be accepted in the absence of supporting evidence showing a variation in rates of differentiation between treated and untreated cells. Relevant literature reports ultrasound treatments increasing gene expression. For example Wu et al teach applying low frequency ultrasound to cultures of primary chondrocytes, resulting in significantly increased levels of aggrecan mRNA levels and proteoglycan synthesis without altering chondrocyte maturation or proliferation. Similarly, Parvizi et al teach applying low frequency ultrasound to chondrocyte cultures and reports no increase in cell number, between ultrasound treated groups

and control groups, but did report significant increases in aggrecan mRNA per cell in group treated with ultrasound (See pg 491, col. 2 – pg 492, col. 1). Generally, the art acknowledges that low frequency ultrasound will increase aggrecan expression in chondrocytes; therefore increased expression of aggrecan does not correlate to accelerated d differentiation of undifferentiated mesenchymal cells to chondrocyte cells, rather it is an inherent result of the ultrasound treatment.

Response to Amendment

Applicant's arguments filed 11/24/04 have been fully considered but they are not persuasive.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Applicant's amendment of claim 1 to read, "A method of accelerating the differentiation of undifferentiated mesenchymal cells to chondrocyte cells, said method comprising culturing undifferentiated mesenchymal cells in a differentiation inducing medium, and irradiating said undifferentiated mesenchymal cells with ultrasound to accelerate the differentiation of said undifferentiated mesenchymal cells to chondrocyte cells" are accepted. The amendments obviate the rejections of claims 1-3 under 35 U.S.C. § 112, second paragraph. Cancellation of claims 4-6 and 10-12 renders the rejections under 35 U.S.C. § § 112, second paragraph, 102, and 103 moot.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

> the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Applicant argues that the prior art does not teach or suggest irradiating undifferentiated mesenchymal cells with ultrasound, as required by claim 1, as Parvizi et al and Nishikori et al all teach applying ultrasound to cultures of differentiated chondrocytes. However, it is asserted that the purpose of the ultrasound is to increase aggrecan and protein expression by the cells, which applicant correlates to accelerating the differentiation of undifferentiated mesenchymal cells to chondrocytes. Applicant demonstrates differentiation of undifferentiated mesenchymal cells to chondrocytes by production of aggrecan proteins; therefore once aggrecan is produced, the cells are considered by applicant to be chondrocytes, and thus once aggrecan is produced the ultrasound is being applied to what applicant is considering chondrocyte cells. It has been clearly taught in the prior art that ultrasound application to cultures of chondrocytes increases aggrecan production (See, e.g., Parvizi et al and Nishikori et al).

Applicant further argues that no motivation has been provided to combine the teachings of Pittenger et al with either Parvizi et al or Nishikori et al; instead applicant argues that the teachings of Parvizi et al and Nishikori et al "teach away" from the combination of the references, citing *In re Grasselli*. The examiner has provided a *prima facie* case of obviousness by combining the teachings of Pittenger et al with that of Parvizi et al or Nishikori et al; Pittenger et al teach the same differentiation medium as used in the current application to successfully induce differentiation of undifferentiated mesenchymal cells to chondrocytes, Parvizi et al and Nishikori et al teach application of ultrasound to cultures of chondrocytes to increase aggrecan and protein production, which applicant correlates to accelerated differentiation of undifferentiated mesenchymal cells to chondrocytes. Examiner asserts that one of ordinary skill in the art would have been motivated to apply ultrasound to undifferentiated mesenchymal cells in a chondroinductive medium that are intended to differentiate into chondrocytes because the

chondroinductive medium has been taught to effect the differentiation into chondrocyte cells, and ultrasound is well known in the art to increase aggrecan production in chondrocytes (See, e.g. Parvizi et al and Nishikori et al). By applying ultrasound directly to a culture of undifferentiated mesenchymal cells that are differentiating into chondrocytes, due to the chondroinductive medium, one ensures that newly differentiated chondrocytes are immediately exposed to the ultrasound, thereby optimizing the protocol by ensuring maximum exposure time to the ultrasound. Additionally, by applying the ultrasound from the beginning of the culture period one would save a step of separating the differentiated chondrocytes and then sequentially applying the ultrasound

Still further, for a rejection under 35 U.S.C. § 103 it is not required that a single reference teach all the limitations of the invention, but rather the combination of references renders the whole invention *prima facie* obvious.

Applicant still further argues that Parvizi et al and/or Nishikori et al "teach away" from the claimed subject matter, and reference the case *In re Grasselli*. The fact pattern of *In re Grasselli* and the fact pattern of the present case are significantly different, and the court decision is not binding with respect to the instant rejection. In *In re Grasselli* the McClellan Patent specifically taught sodium and potassium are undesirable in the catalyst composition, there was specific negative teachings towards claimed components of the applicant's invention. Neither Parvizi et al nor Nishikori et al teach that ultrasound cannot be applied to undifferentiated mesenchymal cells, or that adverse effects occur with the application of ultrasound to undifferentiated mesenchymal cells; therefore they do not "teach away" from the claimed embodiment. Again it is asserted that the ultrasound energy is well known to increase aggrecan production when applied to chondrocyte cells, as was performed in the present application (See, e.g. Parvizi et al and Nishikori et al).

Applicant further argues unexpected advantageous results were obtained make the claimed method non-obvious over similar methods disclosed by the combination of Pittenger et al in view of Parvizi et al or Nishikori et al. Applicant argues that their showing of increased aggrecan production in cultures exposed to ultrasound compared to cultures not exposed to ultrasound constitute unexpected and advantageous results. However these results are not considered unexpected, for the teachings of Parvizi et al and Nishikori et al clearly teach ultrasound increases aggrecan production. Parvizi et al show increased aggrecan and proteoglycan production (See Fig. 4B and 5); though no numbers are provided it is clear that within only six days aggrecan and proteoglycan production was significantly increased. Similarly, Nishikori et al show chondroitin sulfate production, which they correlate to aggrecan production, to be more than twice as great in ultrasound treated cell versus non-treated cells (See Table 1). Therefore the results obtained by applicant were not unexpected; Parvizi et al and Nishikori et al both teach ultrasound increases aggrecan production.

Claims 1 and 2 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Pittenger et al (WO 98/32333-A1) in view of Parvizi et al.

Applicant's claim 1 is directed to a method of accelerating the differentiation of undifferentiated mesenchymal cells to chondrocyte cells; comprising culturing undifferentiated mesenchymal cells in a differentiation inducing medium, and irradiating said undifferentiated cells with ultrasound. Claim 2 requires the ultrasound to have a frequency of 20kHz to 10 MHz, a burst width of 10 usec to 1 msec, a repetition rate of 5 Hz to 10 kHz, and an ultrasound intensity of 5-120 mW/cm^2. Applicant demonstrates the manufacturing of cartilage by increasing production of aggrecan protein (See spec. pg 9). Applicant demonstrates the acceleration of cartilage differentiation induction by increasing production of aggrecan proteins (See spec, pg 9).

Pittenger et al teaches manufacturing artificial cartilage, comprising culturing undifferentiated mesenchymal stem cells in a chondroinductive medium that contains TGF-β3 (See pg 16). Pittenger et al teach the undifferentiated cells developing into a culture of chondrocyte cells (See pg 4).

Pittenger et al do not teach irradiating cells with ultrasound.

Parvizi et al teach irradiating cultures of chondrocyte cells with ultrasound to increase aggrecan mRNA and protein by the chondrocytes, which applicant is calling artificial cartilage (Claim 1) (See pg 491, col. 2). Parvizi et al also teaches using an ultrasound treatment having a frequency of 1.0 MHz, a burst width of 200 usec, a repetition rate of 1.0 kHz, and an ultrasound intensity of 50 and 120 mW/cm^2 (two separate treatment groups) (Claim 2) (See pg 489, col. 2). It would have been obvious to the person of ordinary skill in the art at the time the invention was made to irradiate the culture of chondrocytes with ultrasound. The person of ordinary skill in the art would have been motivated to develop cultures of chondrocytes and then irradiate the culture of with ultrasound in order to upregulate gene and protein expression (See pg 492, col. 2) to promote tissue generation. One would expect success because use of ultrasound to stimulate biological responses such as gene and protein expression, especially aggrecan production in chondrocytes, is a common practice in the art (See for example, Parvizi et al). Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 1-3 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Pittenger et al (WO 98/32333-A1) in view of Nishikori et al.

Applicant's claim 1 is directed to a method of accelerating the differentiation of undifferentiated mesenchymal cells to chondrocyte cells; comprising culturing undifferentiated mesenchymal cells in a differentiation inducing medium, and irradiating said undifferentiated

cells with ultrasound. Claim 2 requires the ultrasound to have a frequency of 20kHz to 10 MHz, a burst width of 10 usec to 1 msec, a repetition rate of 5 Hz to 10 kHz, and an ultrasound intensity of 5-120 mW/cm^2. Applicant demonstrates the manufacturing of cartilage by increasing production of aggrecan protein (See spec. pg 9). Applicant demonstrates the acceleration of cartilage differentiation induction by increasing production of aggrecan proteins (See spec, pg 9).

Pittenger et al teaches manufacturing artificial cartilage, comprising culturing undifferentiated mesenchymal stem cells in a chondroinductive medium that contains TGF-β3 (See pg 16). Pittenger et al teach the undifferentiated cells developing into a culture of chondrocyte cells (See pg 4).

Pittenger et al do not teach irradiating cells with ultrasound.

Nishikori et al teach irradiating cultures of chondrocyte cells with ultrasound to increase aggrecan expression by the chondrocytes, which applicant is calling artificial cartilage (Claim 1) (See pg 202, col. 1). Nishikori et al also teaches using an ultrasound treatment having a frequency of 1.5 MHz, a burst width of 200 usec, a repetition rate of 1.0 kHz, and an ultrasound intensity of 30 mW/cm^2 to promote proliferation (See pg 202, col. 2) (Claims 2 and 3). It would have been obvious to the person of ordinary skill in the art at the time the invention was made to develop cultures of chondrocytes and then irradiate the culture with ultrasound. The person of ordinary skill in the art would have been motivated to irradiate the culture of chondrocytes with ultrasound in order to increase aggrecan production by chondrocytes in articular cartilage for tissue generation. One would expect success because use of ultrasound to stimulate a biological response by influencing cell activity, such as increasing gene and protein expression, especially aggrecan production in chondrocytes, is a common practice in the art (See for example, Nishikori et al). Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Allison M Ford whose telephone number is 571-272-2936. The examiner can normally be reached on M-F 7:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Allison M Ford
Examiner
Art Unit 1651